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(54) Title: NOVEL COMPOSITIONS OF POTASSIUM CHANNEL OPENERS AND PROTEIN KINASE C INHIBITORS AND USE THEREOF

(57) Abstract: Novel compositions comprising one or more potassium channel openers, such as minoxidil, and one or more protein kinase C inhibitors, such as procyanidin B2. Also presented are methods for using the novel compositions for treating and preventing hair loss in a region of a patient.

NOVEL COMPOSITIONS OF POTASSIUM CHANNEL OPENERS AND PROTEIN KINASE C INHIBITORS AND USE THEREOF

Field of the Invention

The present invention relates to novel compositions of potassium channel openers and protein kinase C inhibitors, methods for making the compositions, and methods for inducing and/or stimulating hair growth and/or reducing hair loss using the compositions. The present invention also relates to a first composition comprising one or more potassium channel openers and a second composition comprising one or more protein kinase C inhibitors, said first and second compositions to be used in combination for inducing and/or stimulating hair growth and/or reducing hair loss.

Background of the Invention and Prior Art

Several potassium channel openers (PCOs), also called potassium channel agonists, have been shown to promote hair growth both in animals and humans with androgenetic alopecia. Examples of such PCOs are pinacidil, the pinacidil analogue P-1075 being N-cyano-N-tertpentyl-N'-3-pyridinylguanidine, diazoxide, cromakilim and minoxidil. See Buhl AE, Conrad SJ, Waldon DJ, Brunden MN. Potassium channel conductance as a control mechanism in hair follicles. J Invest Dermatol 1993; 101 (1 Suppl): pp. 148S-152S, and Harmon CS, Lutz D, Ducote J. Potassium channel openers stimulate DNA synthesis in mouse epidermal keratinocyte and whole hair follicle cultures. Skin Pharmacol 1993; 6: 170-178. These PCOs have also vascular effects in that they relax smooth muscle cells of capillaries. This property has been implicated as a possible mechanism for stimulating hair growth by increasing blood supply to the hair follicles, but other mechanisms as well have been suggested for the hair growth stimulant minoxidil.

Such mechanisms are anti-fibrotic effect by its inhibition of lysyl hydroxylase (Murad S, Pinell SR. Suppression of fibroblast proliferation and lysyl hydroxylase activity by minoxidil. J. Biol Chem 1987;262:11973-78), stimulation of keratinocytes (Harmon CS, Lutz D, Ducote J. Potassium channel openers stimulate DNA synthesis in mouse epidermal keratinocyte and whole hair follicle cultures. Skin Pharmacol 1993; 6: 170-178, and Boyera N, Galey I, Bernard BA. Biphasic effects of minoxidil on the proliferation and differentiation of normal human keratinocytes. Skin Pharmacol 1997; 10: 206-220), stimulation of various growth factors (Lachgar S, Charveron M, Gall Y, Bonafe JL. Minoxidil upregulates the expression of vascular

endothelial growth factor in human hair dermal papilla cells. Br J Dermatol 1998; 138: 407-411, and Yamazaki M, Tsuboi R, Lee YR, Ishido K, Mitsui S, Ogawa H. Hair cycle-dependent expression of hepatocyte growth factor (HGF) activator, other proteinases, and proteinase inhibitors correlates with the expression of HGF in rat hair follicles. J Invest Dermatol Symp Proc 1999; 4: 312-315), reduced collagen synthesis (Lachgar S, Charvéron M, Bouhaddioui, Eveux Y, Gall Y, Bonafé. Inhibitory effects of bFGF, VEGF and minoxidil on collagen synthesis by cultured hair dermal papilla cells. Arch Dermatol Res 1996; 288: 469-473) and activation of the cytoprotective prostaglandin PGHS-1 (Michelet JF, Commo S, Billoni N, Mahe YF, Bernard BA. Activation of cytoprotective prostaglandin synthase-1 by minoxidil as a possible explanation for its hair growth-stimulating effect. J Invest Dermatol 1997; 108: 205-209).

Minoxidil (being 2,4-diamino-6-piperidinylpyrimidine-3-oxide) is the active ingredient of Loniten® and Rogaine®, which are marketed by Pharmacia as a treatment for hypertension, and as a treatment and preventative for androgenic alopecia (male and female pattern baldness), respectively. The preparation and antihypertensive use of minoxidil is described in US Patent No 3,461,461. Methods and topical preparations for using the compound to grow hair and to treat male and female pattern baldness are described and claimed in US Patents No 4,139,619 and 4,596,812.

It has recently been shown that several selective protein kinase C inhibitors promote hair growth. See Takahashi T, Kamimura A, Shirai A, Yokoo Y. "Several selective protein kinase C inhibitors including procyanidins promote hair growth". Skin Pharmacol Appl Skin Physiol 2000; 13: 133-142 and Harmon, Charles S., Nevins, Thomas D. "Bisindolylmalemide protein-kinase-C inhibitors delay the decline in DNA synthesis in mouse hair follicle organ cultures." Skin Pharmacol. (1997), 10(2), 71-78. Among those are found calphostin C, procyanidin C1, hexadecylphosphocholine, palmitoyl-DL-carnitine chloride, polymyxin B sulfate, and procyanidin B2. Those molecules have all showed marked anagen induction *in vivo* and have not been associated with potassium channel agonism. When phenolic compounds extracted from plants were investigated for possible hair growth it was found that proanthocyanidins were capable to induce anagen phase. Proanthocyanidins are polymers or oligomers of flavan-3-ol units, such as catechin, epicatechin, gallocatechin, epigallocatechin, afizelechin, and epiafzelechin; whose molecules occasionally incorporate gallic acid. See Porter LJ. Flavans and proanthocyanidins. In The Flavonoids: Advances in Research Since 1986, ed Harborne JB, pp. 23-55. Chapman and Hall, London 1994, and Takahashi T, Kamimura A, Shirai A, Yokoo Y.

"Several selective protein kinase C inhibitors including procyanidins promote hair growth." Skin Pharmacol Appl Skin Physiol 2000; 13: 133-142.

Epicatechin dimers such as procyanidin B1, B2, and B3 as well as the epicatechin trimer C1 but not the monomer show stimulation of hair keratinocytes and hair growth stimulation in the C3H mouse. See Takahashi T, Kamiya T, Hasegawa A, Yokoo Y. Procyanidin oligomers selectively and intensively promote proliferation of mouse hair epithelial cells *in vitro* and activate hair follicle growth *in vivo*. J Invest Dermatol 1999; 112: 310-316.

Use of proanthocyanidine as hair growth promoter is disclosed in WO 9600561.

There are disclosed combination products comprising a potassium channel opener and some other hair promoting agent, e g minoxidil and the 5-alpha reductase inhibitor finasteride, US 5,578,599, and minoxidil and the androgen receptor RU 58841, US 5,411,981.

Anyhow, nowhere is disclosed to combine one or more potassium channel openers and one or more protein kinase C inhibitors.

By combining in a formulation one or more potassium channel openers and one or more protein kinase C inhibitors, which are characterized by different mechanisms of action, an increased hair growth stimulation is achieved in comparison to having just one of the two compound types in the formulation. The two compound types can be mixed and combined in a topical product for treatment of hair loss. The present invention is directed to these, as well as other, important ends. The disclosures of each patent, patent application and publication cited or described in this document are hereby incorporated herein by reference, in their entirety.

Summary of the Invention

The present invention is directed to first novel compositions of one or more potassium channel openers and one or more protein kinase C inhibitors. Specifically, in one embodiment, there is provided a composition comprising minoxidil and procyanidin B2.

Other embodiments of the invention relate to first compositions comprising combinations of other potassium channel openers and other protein kinase C inhibitors.

Further embodiments of the invention relate to a second composition comprising one or more potassium channel openers and a third composition comprising one or more protein kinase C inhibitors, said first and second compositions to be used in combination for inducing and/or stimulating hair growth and/or reducing hair loss.

Methods for treating and/or preventing hair loss in a region of a patient, wherein the methods comprise topically administering to the region compositions as described herein, are

also provided by the present invention.

These and other aspects of the invention will become more apparent from the present disclosure and claims.

Detailed Description of the Invention

The present invention is directed, in part, to novel first compositions of one or more potassium channel openers and one or more protein kinase C inhibitors, to methods for making the compositions, and to methods for inducing and/or stimulating hair growth and/or reducing hair loss using the compositions. The present invention also relates to a second composition comprising one or more potassium channel openers and a third composition comprising one or more protein kinase C inhibitors, said second and third compositions to be used in combination for inducing and/or stimulating hair growth and/or reducing hair loss.

As noted above, the preparation and antihypertensive use of minoxidil is described in US Patent No 3,461,461, and topical preparations and methods relating to the use of the compound to grow hair and to treat androgenic alopecia are described and claimed in US Patents No 4,139,619 and 4,596,812. The disclosures of these three patents are hereby incorporated herein by reference, in their entireties.

As noted above the use of protein kinase C inhibitors for treating alopecia is disclosed in captioned Takahashi et al 1999 and 2000.

The compositions of the present invention may take a variety of forms including, for example, solutions, emulsions, suspensions or mixture thereof in a wide range of viscosities, including semi-solids, in gelled or non-gelled form, for direct topical application or for topical application by spraying, and different forms of patches for topical application.

The respective concentration of the one or more potassium channel openers and the one or more protein kinase C inhibitors in the present compositions may vary within a wide range depending on the specificity for the respective compound and the pharmaceutical formulation used. Useful concentrations are though from around 0.5% (w/w) to around 10% (w/w) when the potassium channel opener minoxidil and from around 0.1% (w/w) to around 10% (w/w) when the protein kinase C inhibitor is procyanidin B2.

A wide variety of solvents may be used in the compositions of the present invention. Preferably, the solvent is a polar solvent. Preferred among these are polar, protic solvents. Preferably, the solvent is water or a hydroxy compound, i e, a compound containing at least one hydroxy (OH) group. Preferred among the hydroxy compounds are alcohols (i e, compounds

containing one hydroxy group) or polyols (i e, compounds containing two or more hydroxy groups) or mixtures of alcohols and/or polyols. Exemplary alcohols include, for example, ethanol, propanol and butanol. Reference herein to "ethanol" includes absolute alcohol, as well as "alcohol USP" and all denatured forms of 95% ethanol. As used herein, the term "propanol" refers to all isomeric forms, including n-propanol and isopropanol, and the term "butanol" refers to all isomeric forms, including, for example, n-butanol, iso-butanol and sec-butanol. Preferred among these alcohols are ethanol and propanol, with ethanol being more preferred. Exemplary polyols include, for example propylene glycol, dipropylene glycol, hexylene glycol, 1,3-butylene glycol, liquid polyethylene glycols, such as polyethylene glycol 200 (PEG-200) and polyethylene glycol 400 (PEG-400), and glycerol (the latter also referred to sometimes as glycerine). Preferred among these polyols is propylene glycol. In a particularly preferred embodiment, the solvent employed may be a mixture of water, an alcohol and a polyol.

The compositions of the present invention may be topically administered to a region of a patient for the prevention or treatment of hair loss. Accordingly, as would be apparent to one of skill in the art, once armed with the teachings of the present disclosure, the compositions may optionally comprise additional pharmaceutically acceptable additives and ingredients such as, for example, pH modifiers, chemical stabilizers, including antioxidants, hair conditioners, such as vitamin B5/panthenol, calcium pantothenate or other panthenol derivatives, colorants, fragrances, fragrance modifiers, other vitamins such as vitamin E, penetration modifiers, such as azone and DEET, surfactants, such as Cremophor® (BASF), cosmetic agents for the skin or scalp, such as fatty acids and fatty acid esters, herbal extracts, such as henna, other viscosity enhancing or thickening agents, oils, emulsifiers, wetting agents, sunscreens and anti-irritants.

A wide variety of methods may be used for preparing the compositions of the present invention. Broadly speaking, the compositions may be prepared by combining together the components of the compositions, as described herein, at a temperature and for a time sufficient to preferably provide a pharmaceutically elegant composition. The term "combining together", as used herein, means that all of the components of the compositions may be combined and mixed together at about the same time. In certain preferred embodiments, the term "combining together" means that the various components may be combined in one or more preferential sequences to provide the desired product.

The compositions of the present invention may be advantageously employed to treat and/or prevent a region of hair loss or alopecia in a patient. Generally speaking, the methods may

comprise topically administering to the region a composition as described herein. The life of a hair is subjected to a cycle, called the pilar cycle, during which the hair grows (anagen), transitions (catagen), and falls out (telogen), before being replaced by a new hair which appears in the same follicle and the cycle is repeated. This constant renewal process undergoes a natural change during ageing. The hair cycles become shorter, resulting in finer, shorter hairs. Hair loss results when this process is accelerated or disturbed, i.e. the growth phases become shorter, the passage of hair into the telogen phase is earlier and hairs fall out in larger numbers. Successive shortening growth cycles may result in increasingly fine and short hair, which is slowly converted into fluff. This phenomenon may lead to progressive hair thinning and may eventually lead to baldness.

Dermatologists recognize many different types of hair loss, the most common by far being androgenetic alopecia (also known as male or female "pattern baldness"), wherein humans begin losing scalp hair as they get older. While this type of hair loss is more common in males, it also occurs in women. This male type of alopecia may be characterized by progressive thinning, as discussed above, or may be characterized by hair loss with little diffuse hair thinning, such as frontal hair loss, mid-anterior balding, bitemporal recession, and/or vertex balding. In females, the androgenetic alopecia is generally characterized by a diffuse thinning of the top of the scalp but with preservation of a frontal hairline. Alopecia areata, anagen hair loss, and diffuse alopecia, such as telogen effluvium are other presentations of hair loss, which may be distinguished from androgenetic alopecia. These other forms of hair loss may also be treated with the present compositions.

The invention is further described in the following examples. These examples are for illustrative purposes only, and are not to be construed as limiting the appended claims.

In the absence of explicit statements to the contrary, as used herein expressions like "comprising", "including", "having", "with" and similar terminology shall not be understood to be exclusively restricted to recited element, but shall be understood to allow for the presence of further elements as well, and shall be understood to cover any element in integral, sub-divided or aggregate forms, as well to imply the inclusion of a stated integer or step or group of integers or steps, but not the exclusion of any other integer or step or group of integers or steps.

As compositions according to the present invention have a better hair growing effect than compositions comprising either only potassium channel openers or only protein kinase C inhibitors it is possible, in order to achieve the same effect, to administer the present

compositions less frequently than had instead been administered a composition comprising either only potassium channel openers or only protein kinase C inhibitors. Useful administration of the present compositions hence includes administration once daily or even less often.

At least additive effect

Use of compositions according to the present invention preferably, but not exclusively, provides for an effect being at least additive in relation to separate use of potassium channel openers and protein kinase C inhibitors respectively. Such additive effect is far from obvious.

There are many examples on drug interaction causing reduced effect of drugs being administered together. Such interaction may take place in the formulation as such. More common is though that the interaction takes place during absorption, during binding to certain receptors and/or during metabolism. An example on formulation-induced interaction is the small or negligible fluorine effect from the early fluorine tooth pastes due to a reaction between the fluorine salt and the calcium of the tooth paste. Examples on inhibition during absorption is the complexation between different antiobiotics and calcium, in e g milk. Reduced effect due to interaction on receptor level is typically seen between the transmittor substances acetylcholine and atropine.

Several interactions between topically administered minoxidil and other topical drugs have been identified. In one study by Fiedler et al (1990) was observed a strongly increased absorption of minoxidil for some patients when minoxidil was used together with anthraline, an anti-inflammatoric substance used to treat psoriasis, but also used to treat alopecia areata. In another study by Ferry and Fiedler (1990) was observed that the absorption of minoxidil was reduced when concomitantly was used the cortisone cream Betamehason. In still another study by Ferry et al (1990) was shown that the absorption of minoxidil was increased when a 2% minoxidil solution was topically co-administered with a dermal preparation comprising vitamin A.

The time during which minoxidil acts on the hair follicles governs the hair stimulating effect of minoxidil. If minoxidil disappears too rapidly from the skin its effect is reduced. If absorption is reduced due to e g a change in pH the effect of minoxidil on the hair follicles will also be reduced.

Minoxidil is a potassium channel opener. It has been shown that certain other potassium channel openers also have a hair growth stimulation effect. Thus, if minoxidil would be

combined with a substance having a similar mode of action no added effect would be expected as the upper limit for this effect would have been reached through the use of minoxidil only.

It might though be possible to achieve an at least additive effect if minoxidil be combined with a substance having another mode of action. This other substance should neither inhibit minoxidil in the formulation, nor counteract minoxidil as to absorption, receptor binding and metabolism. In other words, a non-obvious and inventive process has been performed in order to secure that the necessary conditions are fulfilled in order to preferably achieve an at least additive effect by combined use of potassium channel openers and protein kinase C inhibitors.

Examples

Example 1

Preparation of Solution 1

500 mg minoxidil, 200 mg procyanidin B2, 5.0 g propyleneglycol, 3.0 ml ethanol and purified water to make 10 ml was mixed at room temperature. The mixture was stirred until a clear reddish-brown solution was obtained.

Example 2

Preparation of Solution 2

A batch of 100 ml was obtained by mixing 0.3% (w/w) procyanidin B2, 2.0% (w/w) minoxidil, 70% (w/w) ethanol, 10% (w/w) 1,3-butylene glycol and 18% (w/w) purified water was mixed and stirred at room temperature to obtain a clear reddish-brown solution.

Example 3

Preparation of alternative solutions

As alternatives to Solution 1 and Solution 2 are manufactured solutions essentially in accordance with Examples 1 and 2 wherein the solvent(s) instead are chosen from the list of suitable solvents on page 4.

Example 4

Preparation of alternative embodiments

As alternatives to solutions according to Examples 1, 2 or 3 may be manufactured a second composition comprising one or more potassium channel openers and a third composition comprising one or more protein kinase C inhibitors, said first and second compositions to be used in combination for inducing and/or stimulating hair growth and/or reducing hair loss. Said second and third compositions are manufactured essentially according to Examples 1, 2 or 3.

Said second and third compositions may be administered in many different dosage regimes, e g concomitantly or irrespective of one another. For example a patient may administer one dose from each composition in the morning and one dose from each composition in the evening. Alternatively a patient may administer one dose from the second composition in the morning and one dose from the third composition in the evening. Also other regimes are envisageable, such as different number of doses per day for the second and the third composition respectively. The most suitable administration regime depends on the factual therapeutic situation.

Example 5

Analysis of minoxidil

The quantitative determination of minoxidil was performed by means of a HPLC method using a column (Symmetry™), C18, 3.5 µm, 100 Å, 150 x 4.6 mm and a water/ methanol/glacial acid (30/70/1) mobile phase with 3 g/l of docusate sodium and adjusted to pH 3.0 using perchloric acetic acid. The flow was 1.0 ml/min. the injection volume 20 µl and detection was done at 254 nm using an UV-detector.

1.0 ml of sample was diluted to 100 ml with ethanol and an aliquot of this mixture was diluted 1:50 with mobile phase. A standard solution contained 10 µg/ml of minoxidil. Sample and standard solution were injected and the content of minoxidil calculated based on peak response.

Example 6

Analysis of procyanidin B2

Qualification of procyanidin B2 was performed by means of a HPLC method using a column (Symmetry™), C18, 3.5 µm, 100 Å, 150 x 4.6 mm and a water/ acetonitrile/glacial acid (93:5.2) mobile phase. The flow was 1.0 ml/min. the injection volume 10 µl and detection was done at 280 nm using an UV-detector.

0.5 ml of sample was diluted to 25 ml with mobile phase. A standard solution contained 50 µg/ml of procyanidin B2. Sample and standard solution were injected and the content of procyanidin B2 calculated based on peak response.

Example 7

Stability of Solution 1 and Solution 2 is disclosed below in Table 1 and Table 2 respectively.

Table 1

Solution 1			
Time	Temperature	Minoxidil, mg/ml	Procyanidin B2, mg/ml
Initial		50.2	10.0
1 week	8°C	49.1	9.5
2 weeks	8°C		9.7
6 weeks	8°C	51.1	
8 weeks	8°C		10.0
1 week	25°C	49.1	9.6
2 weeks	25°C		9.5
6 weeks	25°C	51.0	
8 weeks	25°C		9.1

Table 2

Solution 2		
Time	Temperature	Minoxidil, mg/ml
4 weeks	5°C	19.4
4 weeks	25°C	19.3
4 weeks	40°C	19.7

The above results show that stable products are obtained.

Monkey study

The stumptail macaque monkey is used for testing effect of the substances on hair growth. This species show general androgenetic alopecia of the frontal area of the scalp already from the age of two years and has been shown to respond with hair growth to both topical

minoxidil and oral finasteride. In contrast to mice stumptail macaque monkeys are the most universal model animals in this therapeutic area responding both to hormonal and non-hormonal hair growth promoting substances.

A one square inch test area is marked by tattooing dots at the corners of the square. At baseline the test area is shaved and after each month for 4 months the test area is shaved and the weight of the hair is measured. The hair weight is a measure of hair growth. The monkeys are studied in three groups with at least 5 animals in each group. The products tested in the three arms are a) 5% topical minoxidil, b) 1% topical procyanidin B2, c) a mixture of 5% minoxidil and 1% procyanidin B2 manufactured in the same way as Solution 1 of Example 1.

Various modification of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

CLAIMS

1. A first composition comprising one or more potassium channel openers and one or more protein kinase C inhibitors.

2. A set consisting of a second composition comprising one or more potassium channel openers and a third composition comprising one or more protein kinase C inhibitors.

3. A first composition of claim 1 or a set of claim 2 comprising one potassium channel openers and one protein kinase C inhibitors.

4. A first composition or a set of anyone of preceding claims, wherein said one or more potassium channel openers is one or more of pinacidil, diazoxide, cromakilim, minoxidil and/or analogs, salts or derivatives of these compounds.

5. A first composition or a set of anyone of claims 1 to 4, wherein said one or more protein kinase C inhibitors is one or more of calphostin C, hexadecylphosphocholine, palmitoyl-DL-carnitine chloride, polymyxin B sulfate, proanthocyanidins being polymers or oligomers of flavan-3-ol units, such as catechin, epicatechin dimers such as procyanidin B1, B2, and B3, epicatechin trimer C1, gallocatechin, epigallocatechin, afizelechin, epiafzelechin and/or analogs, salts or derivatives of these compounds.

6. A first composition or a set of anyone of the preceding claims which comprises minoxidil and procyanidin B2 or analogs, salts or derivatives and procyanidin B2 or analogs, salts or derivatives thereof.

7. A first composition or a set of claim 6 wherein minoxidil or analogs, salts or derivatives thereof is present in from about 0.5% (w/w) to about 10% (w/w) and procyandin B2 or analogs, salts or derivatives thereof is present in from about 0.1% (w/w) to about 10% (w/w).

8. A first composition or a set of anyone of the preceding claims wherein is/are used solvents chosen from water or a hydroxy compound, preferably alcohols or polyols.

9. A first composition or a set of claim 8 wherein is/are used solvents chosen from water or ethanol, propanol, butanol, propylene glycol, dipropylene glycol, hexylene glycol, 1,3-butylene glycol, liquid polyethylene glycols, such as polyethylene glycol 200 (PEG-200), polyethylene glycol 400 (PEG-400), and glycerol.

10. A first composition or a set of anyone of the preceding claims comprising minoxidil and procyanidin B2 dissolved in a mixture of propyleneglycol, ethanol and water.

11. A first composition or a set of anyone claims 1 - 9 comprising minoxidil and procyanidin B2 dissolved in a mixture of ethanol, 1,3-butylene glycol and water.

12. A first composition or a set of anyone claims 1 - 9 comprising minoxidil and procyanidin B2 dissolved in a mixture of ethanol, dipropylene glycol and water.

13. A first composition or a set of anyone of the preceding claims, further comprising pharmaceutically acceptable additives and ingredients selected from the group consisting of pH modifiers, chemical stabilizers, including antioxidants, hair conditioners, panthenol derivatives, calcium pantothenate, colorants, fragrances, fragrance modifiers, vitamin E, penetration modifiers, surfactants, cosmetic agents, fatty acids and fatty acid esters, herbal extracts, henna, oils, emulsifiers, wetting agents, sunscreens, and anti-irritants.

14. A first composition or a set of anyone of the preceding claims formulated in one of or a mixture of the following dosage forms: solutions, emulsions, suspensions or mixture thereof, including semi-solids, in gelled or non-gelled form, useful for direct topical application or for topical application by spraying, and patches for topical application.

15. A method for treating or preventing male or female hair loss in a region of a patient, said method comprising topically administering to said region a first composition according to anyone of claims 1 - 14.

16. A method according to claim 15, wherein said hair loss comprises androgenetic alopecia (including frontal hair loss, bitemporal recession, vertex balding and mid-anterior balding), alopecia areata, and diffuse alopecia (including anagen hair loss and telogen effluvium).

17. A method for treating or preventing male or female hair loss in a region of a patient, said method comprising topically administering to said region a second composition and a third composition of a set according to anyone of claims 1 - 13.

18. A method for treating or preventing male or female hair loss of claim 17 wherein the second composition and the third composition are administered concomitantly.

19. A method for treating or preventing male or female hair loss of claim 17 wherein the second composition and the third composition are administered independently of each other.

20. A method according to anyone of claims 17 - 19, wherein said hair loss comprises androgenetic alopecia (including frontal hair loss, bitemporal recession, vertex balding and mid-anterior balding), alopecia areata, and diffuse alopecia (including anagen hair loss and telogen effluvium).

21. A method according to anyone of claims 15 - 20 wherein the administration takes places once-a-day or less frequently than once-a-day.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00105

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61P 7/06, C07D 311/62, A61P 17/14
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, C07D, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Skin Pharmacol, Volume 10, 1997, pages 71-78, Charles S. Harmon et al: "Bisindolylmaleimidine Protein-Kinase-C Inhibitors Delay the Decline in DNA Synthesis in Mouse Hair Follicle Organ Cultures", page 77 --	4-14
X	Acta Derm Venereol (Stockh), Volume 78, 1998, pages 428-432, Tomoya Takahashi et al: "Proanthocyanidins from Grape Seeds Promote Proliferation of Mouse Hair Follicle Cells In vitro and Convert Hair Cycle In vivo" --	4-14

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 April 2002	02 -05- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer FERNANDO FARIETA/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00105

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Skin Pharmacol Appl Skin Physiol, Volume 13, 2000, pages 133-142, Tomoya Takahashi et al: Several Selective Protein Kinase C Inhibitors Including Procyanidins Promote Hair Growth"	4-14
Y	US 5578599 A (DIANI ET AL), 26 November 1996 (26.11.96), column 3; column 4	4-14
A	US 6136969 A (BARBIER ET AL), 24 October 2000 (24.10.00), column 4	4-14
A	US 5914406 A (BARBIER ET AL), 22 June 1999 (22.06.99), column 5, line 61 - column 6, line 44	4-14
A	EP 0797978 A2 (KYOWA HAKKO KOGYO CO. LTD.), 25 March 1997 (25.03.97), page 2, line 5 - line 25, claims 1-6	4-14
A	US 5907038 A (BARBIER ET AL), 25 May 1999 (25.05.99), column 3, line 64 - column 4, line 21	4-14
A	US 4596812 A (CHIDSEY, III ET AL), 24 June 1986 (24.06.86), columns 1,2	4-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/01/02

International application No.
PCT/SE 02/00105

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INTERNATIONAL SEARCH REPORT

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-3
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet*

2. ☒ Claims Nos.: 15-21
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet**

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

*
Claims 1-3 are not clear because the wording "Potassium channel openers and protein Kinase C inhibitors" would include all the known and unknown variants. According to Art 6, a completely search can not be performed.

**
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods. See PCT Rule 39.1(iv)